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Medical Progress

Hip Fracture, Skeletal Fragility, Osteoporosis and Hormonal Deprivation in Elderly Women

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Fractures of the hip have been shown to have a significant personal and societal impact in Western countries; this impact is largely borne by elderly women, and represents a substantial health care commitment in modern society. For many people a fracture of the proximal end of the femur represents a preterminal event of considerable cost, both in economic loss and psychosocial well-being. These fractures are generally recognized as a clinical complication of osteoporosis, and are one index of general skeletal fragility which is also manifested in fractures of the vertebrae and of the distal radius (Colles fracture).

There is increasing evidence that hormonal deprivation in elderly women is directly related to loss of skeletal integrity and consequent fragility. There is also increasing evidence that hormonal substitution is effective in preventing this structural loss and fragility. Unfortunately, a therapeutic dilemma has arisen in that the preparation that seems to give optimal protection, conjugated estrogens, has also been reported to cause an increased incidence of endometrial carcinoma. The search for a preparation or dosage regimen of estrogens which simultaneously prevents skeletal atrophy and fragility and avoids the increased risk of malignancy must be a long-term goal.

FRACTURES OF THE HIP have been shown to have serious personal and social impact and represent a substantial commitment of medical care resources among Western societies. Fractures of the hip in the elderly are associated with all the commonly recognized indices of impaired health (such as disability, discomfort, social disruption and dissatisfaction), frequently lead to fatal complications, and are an index of general skeletal fragility. The impact and effect of these fractures is borne largely by elderly women. Many studies have shown that hip fractures occur more frequently at all ages in women, and increase to as much as nine times as often in women over age 60.[1]

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Impact of Hip Fractures

Wylie,[2] in surveying Medicare data for 1967, found that the rate of femur fracture as measured by discharge diagnoses from acute care hospitals in the United States was 909 per 100,000 white

women 65 years of age and older and enrolled in Medicare, representing an incidence rate of almost 1.0 percent per year. The rate doubled in men and women 80 to 84 years of age, with a ratio of approximately three women to one man overall.

Bauer[1] estimated that in Malmö, Sweden, in 1955 the annual fracture rate for the femoral neck was 220 per 100,000 women between the ages of 65 and 69. This increased to 1,170 per 100,000 women 80 years or older, an incidence rate of almost 1.2 percent per year.

Morgan[3] estimates the frequency of femoral neck fractures in Europe as rising from less than one per 1,000 (per ten-year span) in early life to over 12 per 1,000 by age 90. He further estimates the cumulative probability of fracture of the neck of the femur as approaching 30 percent by age 90, assuming that all persons at risk survive to that age, a disconcerting demographic surmise as longevity increases. Alffram[4] also gives the cumulative risk in Sweden of sustaining at least one cervical or intertrochanteric femoral fracture before age 90 as nearly 25 percent. It must be noted that genetic variations are considerable and northern European gene pools apparently involve substantially increased risk.[5]

Alffram[4] studied 1,664 fractures of the proximal end of the femur in Malmö between 1949 and 1961. The mean age was 73 years in women and 69 years in men, with 86.0 percent of the patients being older than 60. These fractures were 2.4 times more frequent in women, and women who had previously sustained a fracture of the distal radius (Colles fracture), another index of skeletal fragility, were at even greater risk as age advanced. The observed number of fractures of the femur nearly doubled the number expected among women between ages 75 and 79, if preceded by a distal forearm fracture.

Beals[6] studied the incidence of hip fractures in Portland, Oregon, in a population which fairly represents a demographic cross section of at least one half of the major urban areas in the United States. He found that there was a peak incidence at 78 years of age, that 8.5 percent of the cases had already sustained one previous hip fracture, and 4.6 percent had other associated fractures. At the end of one year following the fracture, only 50 percent of these patients remained alive. After four years, only 15.0 percent of the men and 41.0 percent of the women 75 years or older were still alive. These findings confirmed the results of an earlier study in Norway by Mikkelsen and Langholm,[7] which showed greatly increased mortality during the first four years after proximal femoral fractures.

Sweet and co-workers[8] studied associated morbidity and mortality in 53 cases of fractures of the proximal femur. The mortality was 21.7 percent in the transcervical and 16.6 percent in the intertrochanteric group while in hospital. Morbidity was given as 56.5 percent and 60.0 percent, respectively. Newton-John and Morgan[9] came to the following conclusions:

> (1) all persons lose bone with age; (2) there is so far no evidence that osteoporosis in the older population is the result of either an excessive rate of loss or an abnormal total loss of bone; and (3) the risk of fracture is largely determined by the amount of bone, and the increase in frequency of fracture with age is largely determined by the normal loss of bone with age.
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> The increase in the frequency of fractures of the femoral neck is approximately exponential, whereas the loss of bone with age in [sic] linear. Fractures happen in persons with the thinner bones and it follows from the characteristics of bone loss with age, that the frequency of "thin bones" however defined, increases exponentially with age.

Kohn and co-workers,[10] in a study of all patients 80 years and older at the University Surgical Clinic in Vienna, found that 338 of 599 patients, or 56.4 percent who required operations for any reason, required them for hip fractures. An additional 41 or 6.8 percent required operations for other fractures. There were 72 deaths in the hip fracture group. A total of 403 or 83.0 percent of the patients requiring surgical procedures for trauma were women.

Barnes and colleagues,[11] in a large retrospective study of subcapital femoral fractures in Great Britain, found that 395 of the 1,618 patients (24.4 percent) died before the results of the treatment could be evaluated; 7.4 percent of the women and 13.3 percent of the men died within a month of operation. Approximately a third of displaced fractures failed to unite (presumably with increased likelihood of additional operations). The likelihood of nonunion increased with age. Late segmental collapse, presumably on a vascular basis, developed in 24.0 percent of the women and 15.0 percent of the men, and was physically disabling in 29.0 percent of this subset.

Data from the Medicare program[12] can be used to provide evidence of the economic impact of fractures of the neck of the femur among elderly women. In 1973 fracture of the neck of the femur

was the fifth most frequent diagnosis at hospital discharge among women in the program. The mean length of hospital stay for these fractures among women was 22.3 days as compared with a mean length of stay of 11.2 days for all other discharges among both sexes. The mean charge per hospital stay for fractures of the neck of the femur was $2,263 compared with $1,176 for all other diagnoses (given in 1973 dollar amounts). Hospital charges for such fractures among women 65 years and older in the Medicare program in 1973 were estimated to be $212 million. This will undoubtedly increase as more women continue to live longer.

Hip Fractures and Osteoporosis

Hip fractures in the elderly are generally recognized as a clinical complication of osteoporosis. In the early 1820's, Sir Astley Cooper in his *Treatise on Dislocations and on Fractures of the Joints*[13] made the following observations:

> the fracture of the neck of the thigh bone within the capsular ligament seldom happens but at an advanced period of life. . . . That regular decay of nature which is called old age is attended with changes which are easily detected in the dead body; and one of the principal of these is found in the bones, for they become thin in their shell and spongy in their texture. . . . Women are much more liable to this species of fracture than men.

These early and astute observations of the relationships between age, sex, loss of bone substance and fracture of the proximal femur have been amplified and verified by 1½ centuries of subsequent medical research, but to this day there is no consensus on prophylaxis. Our understanding of osteoporosis traces its modern concepts to Fuller Albright, who in 1941 wrote that osteoporosis is a "condition in which there is a lack of bone tissue but that which remains is fully calcified."[14] He believed it was caused by deficient formation of bone.

Osteoporosis is generally recognized as a disease predominantly of the axial skeleton, appearing as a reduction of mass of both cortical and cancellous bone in the vertebrae, ribs, pelvis and the neck of the femur. Both epidemiologic and clinical studies have shown the association between fractures of the neck of the femur, the distal radius and the vertebrae and osteoporosis.

Lender and co-workers[15] examined the prevalence of osteoporosis in Jerusalem between 1967 and 1971 in a general population and among patients with fractures of the neck of the femur. Using identical criteria applied to lateral x-ray films of the lumbar spine they reported a prevalence rate of osteoporosis of 14.5 percent among women in the general population and of 37.8 percent among women with femoral neck fractures.

Iskrant and Smith[16] studied the coincidence of osteoporosis (diagnosed by relative vertebral density determined by lateral roentgenograms of the dorsolumbar spine) and fractures in women aged 45 years and older for a three-year period. The annual fracture rate was 3.6 percent, and varied from 2.0 percent among those without osteoporosis to 7.0 percent in those with the condition. The closest associations were with fractures of the upper femur, radius, ankle and wrists.

Nilsson,[17] in a study of women 50 years and older, showed a significantly lower "head plus trunk height" to "total height" ratio in patients with proximal femoral fractures than in age-matched control patients with a variety of other orthopedic conditions. He also detected significant weight disparity. This association is thought to be a result of shortening of the spine because of vertebral fracture caused by osteoporosis. This has also been shown by Gordan.[18,19]

Urist and colleagues[20] studied 100 postmenopausal white women with radiologic osteoporosis (shown by multiple vertebral fractures) for periods ranging from 7 to 20 years. These women, most of of whom were between 60 and 70 years of age at the time of first observation, were engaged in the usual activities of daily life for their age and sex. Nine sustained at least one long-bone fracture during the observation period and two sustained femoral neck fractures, for an overall fracture incidence of 11 percent.

Alhava and Karjalainen[21] showed that the mean bone mineral content of the trabecular radius was significantly lower than normal in both sexes when the index event was a fracture of the hip. Nordin and co-workers[22] believe that postmenopausal osteoporosis is a self-limiting process in cancellous bone but a continuing process in cortical bone, at least as measured in the metacarpals. They believe the age-related increase in frequency of distal forearm fractures reflects the situation in cancellous bone, and the increase in femoral neck fractures reflects the situation in cortical bone, thus explaining the progressively increased frequency of the latter as age advances.

Reeves[23] studied the uninjured, excised, proximal femur of 37 patients who had died within a

year of metallic prosthetic replacement for fracture of the contralateral hip. All had walked after the replacement. Loading to failure of these femurs was positively correlated with bone mass studies (on both femoral heads) as well as with roentgenographic and postmortem estimations of the thickness of the cortical bone. The results suggested that there is a group of elderly women in whom fracture of the femoral neck may occur under the load (about three times body weight) imposed by quiet walking with a reduced bone mass. Singh and co-workers[24] described changes in the roentgenographic patterns and numbers of trabeculae in the femoral head and neck, which they were able to correlate statistically with histological grading of iliac crest biopsies, the occurrence of femoral head and neck fractures, and the degree of trauma which had caused the fracture. These studies seem to substantiate the notion that loss of bone in the proximal femur occurs as a part of a generalized process (osteoporosis), and predisposes to bone failure under ordinary stresses of walking or stumbling.

Vose and colleagues[25] showed an increased ash content and increased strength per unit volume of cortical bone of osteoporotic femurs, compared with nondiseased femurs, in spite of which the overall strength of the osteoporotic femurs under static loading was reduced by approximately 40 percent. They concluded that the weakness which leads to fractures is a quantitative, and not a qualitative phenomenon, that is, due to "atrophy of the cortical wall." Alhava,[26] in a study of 81 women and 23 men who had sustained hip fractures from moderate or insignificant trauma, concluded that senile osteoporosis was the most important predisposing factor. The mean age of this group of patients was about 72 years.

Loss of Ovarian Function and Bone Mineral Content

Dalen and colleagues[27] assayed the bone mineral content in women who had had oophorectomies and in those who had not had this operation by means of x-ray spectrophotometry in five different parts of the skeleton. They were able to show an average diminution of 18 percent in mineral content of mainly trabecular parts of the skeleton (distal radius and ulna, third lumbar vertebra, femoral neck), in contrast to cortical parts, and concluded that increased fracture risk existed in these areas. Meema and Meema[28] have shown by densitometric and morphometric roentgenographic bone measurements that there is an age-related decline in bone mineral content in women that is progressive. They noted in their study that women of all ages, but especially after age 60, with both vertebral compression fractures and femoral neck fractures fell below the mean for mineral mass and cortical thickness of the radius for their age group. Virtually all fell more than two standard deviations below the mean for younger (less than 50 years) women, whose bone strength can, generally speaking, be assumed to be adequate to the stresses imposed on it.

Dequeker[29] has shown that cortical area, measured by metacarpal width, declines progessively with age in women, and that women with hip fractures fall consistently below the age-adjusted mean regression line for cortical metacarpal width. Interestingly, fractures of the surgical neck of the humerus did not correlate well, while those of the lower end of the radius did. He also was able to correlate, positively, in cadaver specimens, trabecular bone mass of iliac crest specimens and cortical bone mass measured on x-ray films of the right second metacarpal, again suggesting generalized skeletal hypoplasia.

Foss and Byers[30] have also shown that patients with fractures of the upper end of the femur have a less than normal metacarpal index and almost never have osteoarthrosis, which instead correlated with an increased metacarpal index. This confirmed an earlier study[31] done with trephine biopsy photomicrograph specimens of iliac crest bone, which suggested that there was a substantially higher incidence of osteoporosis in patients with femoral neck fractures.

Khairi and co-workers[32] studied the fracture-predicting usefulness of the femoral trabecular index (Singh) and bone mineral measurement by photon absorptiometry in 106 white women 70 to 95 years old. A positive correlation was found between the Singh index and the bone mineral content, but it was not useful in predicting subsequent fractures.

While most data available show that bone loss is related to advancing age, there is also substantial evidence suggesting that bone loss in women is related to loss of ovarian function rather than to aging as such. The extent of bone loss appears to be a function of the number of years after menopause, either natural or surgical. Such findings have been reported by Meema and Meema[28] by comparing bone mineral mass of the radius measured by radiographic photodensitom-

etry in postmenopausal and premenopausal women. Similar conclusions have been reached by Nordin and colleagues,[33] who measured cortical thickness of the second metacarpal; by Aitken and co-workers,[34,35] who assessed radiographic density of the third metacarpal; by Heer and colleague[36] who examined bone mineral mass of the radius with photon absorptiometry; by Dalen and co-workers[27]; by Heaney[37]; and in a sequential study by Nordin and colleagues.[38]

Thus, it appears compelling to this observer that fractures among elderly women, notably compression fractures of the vertebrae, distal radius and proximal end of the femur are the result of loss of bone mass. That bone loss occurs in the proximal femur as age advances has been shown, and that such bones are more prone to fail under stress is also clear. It also appears that loss of bone mass in women is directly related to loss of ovarian function, whether occurring naturally or induced by surgical means; further, the longer the postmenopausal period the greater the loss in bone mass.

Osteoporosis and Estrogen Administration

The apparent relationship between loss of ovarian function and the cause of postmenopausal osteoporosis has led to estrogen therapy being the choice of many workers for both treatment and prevention of postmenopausal osteoporosis. Data to support such use of estrogens have been adduced by Henneman and Wallach,[39] Davis and co-workers,[40] and Meema and Meema.[41] These early studies indicated that estrogen therapy given after oophorectomy may at best only delay the onset of bone mineral loss with age. More recent evidence by Aitken and co-workers[34,42] has shown that relatively small dosages of estrogen will prevent, and if given early enough, will reverse such losses of bone mineral content. In a controlled double-blind study, estrogen therapy (mestranol), started within two months of oophorectomy, effectively prevented bone loss, and started three years, but not later than six years, after oophorectomy caused a highly significant increase in bone mineral content compared with untreated controls.

Meema and co-workers[43] were also able to show a significant preventive effect of estrogen therapy on postmenopausal bone loss both in castrates and following natural menopause in 82 women evaluated twice at four- to ten-year intervals. Those most frequently used were equine conjugated estrogens in doses of 0.625 or 1.25 mg per day. Recker and Heaney[44] studied the cases of 60 postmenopausal women who had been divided into three groups: (1) those receiving no estrogen; (2) those receiving 0.625 of conjugated estrogens and 5 mg of methyltestosterone 21 days of each month, and (3) those receiving 2.6 grams of calcium carbonate per day. In women in the hormone group and the calcium group there was significant diminution in the rate of bone loss when measured by radiography, but protection was noted in those in the hormone group only when measured by photon absorptiometry. Horsman and colleagues[45] confirmed that estrogen administration prevents bone loss in a prospective study of the cases of 72 postmenopausal women followed for two years.

Lindsay and co-workers[46,47] showed that in women who had had oophorectomies continuous estrogen therapy had been effective in preventing bone loss for eight years, the length of their observations. On the other hand, the women who had discontinued estrogen therapy after four years showed the same amount of bone loss as those who had had oophorectomies and who were not receiving estrogen therapy.

Thus, there is substantial evidence accumulating to indicate that estrogen therapy is effective in preventing postmenopausal osteoporosis as measured by a reduction in bone mineral content. It also appears that both the timing and the length of estrogen therapy influence the rate and the amount of bone loss. That estrogen therapy can prevent the clinical complications of osteoporosis, such as fractures of the neck of the femur is also becoming clearer. Hutchinson and co-workers[48] were able to show a protective effect of postmenopausal estrogens, on both hip and distal radius fractures, with an odds ratio of 3.8 if started within five years of menopause.

The Prophylactic Dilemma

Recent reports[49-52] of an increased incidence of endometrial carcinoma, ranging from 4.5 to 12.5 times the expected rate, among long-term estrogen users has resulted in widespread professional concern and likely has diminished the frequency of its use. The effects of estrogens on the endometrium are difficult to interpret, however, and misdiagnosis of adenomatous hyperplasia as endometrial carcinoma, combined with increased scrutiny of estrogen users,[53] may have resulted in an overestimation of the frequency of this problem. Another study[54] of long-term estro-

gen use after hysterectomy has indicated that overall mortality from all causes, including cardiovascular and neoplastic, was lower than expected. Under any circumstances accurate epidemiologic data will be necessary to evaluate the relative risk of death and disability from hip fracture and from malignant conditions. The choice is not clear at this time and remains difficult to make once both sides of the controversy are fully developed.

Additional preparations and lower dosage regimens of conjugated estrogens have also been suggested in the approach to this problem. Geola and associates[55] have recently shown that as little as 0.3 mg of conjugated equine estrogens given orally can cause reversion of the calcium/creatinine ratio to premenopausal levels as early as six weeks after initiation of therapy. The relationship of the calcium/creatinine ratio to bone metabolism, however, is only inferential with regard to the prevention of fracture. It, nonetheless, indicates that a dosage regimen, smaller than that associated with malignant conditions of the uterus, may be effective. In a study by Recker and colleagues[44] conjugated equine estrogens and methyltestosterone were used in one regimen and calcium carbonate in another in menopausal women. When radiographic estimation of metacarpal cortical thickness was carried out, the hormone and the calcium regimens both appeared to show significant reduction in the rate of decrease of skeletal mass. However, when studied by photon absorptiometry only the hormone group showed a significant protective effect compared with controls.

Horsman and co-workers,[45] in a prospective trial of 72 postmenopausal women whose cases were followed at least two years, showed that the group treated with estrogens lost no bone by either densitometry or determination of metacarpal thickness. The calcium-treated group showed intermediate bone loss between that of the control group and that of the estrogen-treated group, thus, indicating less than optimal results from this technique.

Calcitonin has also been suggested as a method of management of osteoporosis; Wallach and colleagues[56] showed in a small series that approximately 50 percent of patients will respond to the use of calcitonin. They found that total body calcium, as measured by in vivo neutron activation analysis, increased in 12 patients; however, an additional 13 treated in the same manner did not change or showed a decrease of total body calcium. In addition, it was noted that antibodies developed in six patients. Chestnut and co-workers[57] studied the cases of women given calcitonin in combination with calcium carbonate and vitamin D_2 for 18 months. They were able to show an increase in total body calcium as measured by neutron activation analysis; however, antibodies were detected in 18 of 26 patients in the treatment group. It seems to this observer that medical history clearly indicates that one must be circumspect about chronic medical treatment with any preparation which is likely to produce immune responses in the patient. Further work is clearly indicated in this area before it can be recommended for use in other than a controlled research setting.

Lindsay and co-workers[58] have shown in a preliminary randomized trial carried out over a year that intramuscularly given progestogen (Gestronol) as well as mestranol can prevent bone mineral loss as measured by photon absorptiometry. More work will be required in this area as well.

The use of fluoride and calcium has also been suggested in the management of osteoporosis. In a recent paper, Riggs and co-workers,[59] reported on the cases of 36 patients with primary osteoporosis who were treated up to six years with sodium fluoride, calcium supplements and, in 24 patients, vitamin D. Major adverse reactions, including synovitis, painful plantar fascial syndrome, recurrent vomiting or anemia occurred in 15 of this group, representing a 42 percent complication rate. New vertebral fractures continued to occur at an alarming rate for at least the first year of therapy, indicating a considerable lag phase if this treatment is effective at all. This group concluded that "until long-term safety and antifracture efficacy are better established, this regimen should continue to be restricted to investigational use."[59]

Conclusion

It appears that the search for a preparation or dosage regimen which simultaneously prevents skeletal atrophy and fragility, and avoids the increased risk of malignancy must be a long-term goal. What is not acceptable is unquestioning subservience to the idea that a possibly increased risk of uterine malignancy must sweep aside all considerations of morbidity and mortality from hip fractures that might be prevented.

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